REMARKS

I. Status of the Claims

Claims 246-252, 255, 264, 265 and 271-275 were pending and examined in the March 10, 2010 Office Action. With this Reply, claim 271 is canceled and 273 is amended. The claim cancellation and amendment is made without prejudice or disclaimer and introduces no new matter. Claims 246-252, 255, 264, 265, 273, 274, 276 and 277 are presented for reconsideration.

II. Rejection under 35 U.S.C. 112, First Paragraph - Written Description

Claim 273 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Office Action asserts that the claim is not supported in the specification and invites the Applicants to identify a location in the specification where the claim elements are described. In response, Applicants point to paragraphs **[382-394]** and FIG. 6 of the specification as published as US 2001/0007767. As further discussed in the cited paragraphs, and with reference to FIG. 6, Applicants point to panel (b), where the claim elements are identified as follows:

Claim Element	Portion of FIG. 6
Non-nucleic acid entity conferring cell targeting	Tri-lactyl moieties (on "third strand")
First strand (template)	"Segment 2"
Second strand – having one segment complementary to a portion of the first strand and second segment lacks complementarity and comprises a polynucleotide tail	"Segment 3" – portion having "F" feature is complementary and noncomplementary portion has polynucleotide tail – a polyA segment complementary to "Segment 4" – the third strand (below)
Third strand – complementary to polynucleotide tail and comprises non-nucleic acid entity	"Segment 4" – complementary to polyA segment of second strand (paragraph **[0394]** says extended with TTP and lactyl-dUTP to form Tri-lactyl moieties; has non-nucleic acid entity "F"

Thus, claim 273 finds support as described above. Applicants therefore respectfully request withdrawal of this rejection.

III. Rejection under 35 U.S.C. 112, Second Paragraph

Claim 273 is rejected under 35 U.S.C., second paragraph, as being unclear. Applicants request reconsideration and withdrawal of this rejection in light of the following comments.

As outlined under **II.** above, claim 273 finds support in the specification. As such, the skilled artisan would be able to understand the structure of the claimed construct by referring at least to paragraphs **[382-394]** and FIG. 6 of the specification as published as US 2001/0007767. Specifically, with regard to the second strand terminus, the skilled artisan would understand that the polynucleotide tail is at least part of the terminus of the strand, as illustrated in FIG. 6. Thus, the cited portions of the specification, including FIG. 6, provide a possible structure of the claimed construct such that each term of the claim is clear and unambiguous. Regarding whether the construct is linear or circular, or comprising nicks, such limitations are not part of the claim. However, Applicants reiterate that the claim would be clear and unambiguous to the skilled artisan referring to the specification.

In light of the above discussion, Applicants respectfully request withdrawal of the rejection of claim 273 under 35 U.S.C. 112, second paragraph.

IV. Rejections under 35 U.S.C. § 102(b)

(a) Claim 271 is rejected under 35 U.S.C. 102(b) as being anticipated by Myers et al. (EP 0 273 085). This rejection is moot since claim 271 is canceled.

V. Rejections under 35 U.S.C. § 103(a)

Claims 246-252, 255, 264, 265, 274 and 276-279 are rejected under 35 U.S.C. 103(a) as being unpatentable over Craig et al. (U.S. 5,766,902) et al., Wagner et al. (U.S. PNAS 1992), and Perales et al. (Eur. J. Biochem., Vol. 226:255-266. The Action asserts that

> Craig et al. taught methods for enhancing the targeted delivery of nucleic acid molecules to cells by coupling the nucleic acid to a ligand having affinity for a cell surface molecule or receptor....Specifically recommended are antibodies, growth factors, and fusogenic peptides.... The ligand may be chemically conjugated by covalent bonded to the nucleic acid....
>
> Wagner et al. teach the use of ligand mediated constructs to deliver DNA to cells and state that delivery from endosomes is a limiting step that can be solved by the additional use of a fusogenic peptide....
>
> Perales et al. discuss the concept of ligand mediated delivery of DNA and outlines the design elements that are useful. Perales et al. teach the DNA ligand needs to be efficiently transported to the nucleus and this active process that requires the use of nuclear localization elements....

Office Action at pp. 7-8. Applicants respectfully request reconsideration and withdrawal of this rejection in light of the following discussion.

Craig et al. teach the use of an electric field to improve the efficiency of receptor mediated DNA uptake.

Wagner et al. teach the conjugation of adenovirus using an anti-adenovirus antibody conjugated to polylysine, where DNA binds to the polylysine noncovalently, and where a receptor may be bound to the polylysine via a biotin-streptavidin linkage (Wagner et al., Abstract). As such, Wagner et al. do not teach or suggest a nucleic acid comprising a modified nucleotide, and instead teaches that polylysine is suitable as an agent to noncovalently bind nucleic acid to a complex. Thus, Wagner et al. teaches that the conjugation of a fusogenic peptide or a ligand to a nucleic acid can be easily achieved using non-covalent nucleic acid binding to polylysine, which does not require the modified nucleotide or nucleotide analog as claimed. Therefore, Wagner et al. teaches away from the instant invention by teaching that a modified nucleotide or

nucleotide analog is not necessary to make a nucleic acid that is associated with a fusogenic peptide or ligand to achieve the benefit of increased transfection or localization of the nucleic acid.

Perales et al. is a review of receptor-mediated gene delivery. Like Wagner et al., Perales et al. teach that a receptor need not be covalently conjugated to a nucleotide, and that "[m]ost methods used to transfer genes into cells via receptors take advantage of the ability of positively charged polypeptides to achieve electrostatic interaction with DNA." Thus, Perales et al. teach away from the claimed methods by indicating that noncovalent use of polylysine is the preferred method to bind nucleic acid to a receptor.

Applicants also note that none of the cited references teach or suggest a nucleic acid construct that comprises more than one targeting moiety such as a fusogenic peptide, a ligand to a cell receptor, and an entity that confers nuclear localization. Further, none of the cited references teach or suggest any part of the construct of claim 273 and the claims dependent thereon.

Based on the above discussion, it is clear that the combination of references do not make the instant claims obvious because (a) none of the cited references teach or suggest a nucleic acid construct with more than one targeting moiety conjugated thereto; and (b) two of the references, Wagner et al. and Perales et al. teach that a receptor-nucleic acid complex need not have the receptor conjugated to a nucleotide to create a modified nucleotide or nucleotide analog, but that the nucleic acid is preferably complexed with the receptor using polylysine. This teaches away from the claimed invention. Further, none of the cited references, alone or in combination, teach or suggest the construct described in claim 273. Withdrawal of the rejection under 35 U.S.C. 103(a) is thus respectfully requested.

VI. Double Patenting

Claims 246-252, 255, 264, 265, 271, 273 and 274 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting (OPD) as being unpatentable over claims 245-248, 251, 253, 261-265, 306 and 307 of copending Application No. 08/978,633. Since this rejection is dependent on the scope of both the instant claims and the claims in the cited application, Applicants will provide terminal disclaimers where necessary when proper ODP rejections are the only rejections remaining in this application.

VII. Conclusion

In view of the foregoing remarks, Applicants respectfully request withdrawal of all rejections and passage of claims 246-252, 255, 264, 265, 273, 274, and 276-279 to allowance.

The United States Patent and Trademark Office is hereby authorized to charge the extension of time, as well as any other fees required to maintain pendency of this application, to Deposit Account No. 05-1135.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney requests that he be contacted at the number provided below.

Respectfully submitted,

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